Approaches to Evaluating UX007 (Triheptanoin) in Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

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Disclaimer

• Dr. Bowden is an Associate Director, Clinical Outcomes Research and Evaluation employed by Ultragenyx Pharmaceutical
Objectives

1. Incorporating the patient perspective in understanding the symptoms and functional impact of Glut1 DS

2. Using qualitative evidence to support the selection/development of meaningful clinical outcome assessments (COAs) for paroxysmal manifestations of Glut1 DS
Topics

• Review of Clinical Outcome Assessments (COAs)
• Understanding Glut1 DS: Qualitative Research
  – Literature review
  – Physician interviews
  – Patient/Caregiver (CG) interviews
  – Patient functional assessment study
• Meaningful COAs for Glut1 DS
What is a Clinical Outcome Assessment?

• Measure of how a patient survives, feels or functions
  – Determine if a drug has been demonstrated to provide a treatment benefit

• Types of Clinical Outcome Assessments
  – Performance Outcomes (PerfO)
  – Patient-Reported Outcome (PRO)
  – Observer-Reported Outcome (ObsRO)
  – Clinician-Reported Outcome (ClinRO)

• Selecting and Developing Clinical Outcome Assessments
  – Use existing measures
  – Modify existing measures
  – Develop novel measures
Performance Outcome (PerfO)

- Measurement based on a task(s) performed by the patient
- Represent an aspect of daily life that is important to the patient
- Requires cooperation and motivation
Patient Reported Outcome (PRO)

- Report of a patient's health condition that comes directly from the patient
  - Symptom severity e.g. pain
  - Perception of daily functioning
  - Feelings of well being
  - Impact/Satisfaction with treatment
  - Health-Related Quality of Life

Source: http://www.ispor.org/meetings/va0502/symposium.asp
Observer Reported Outcome (ObsRO)

- Measurement based on observation by someone other than the patient or clinician e.g. parent or partner
- For patients that are unable to self report
  - Young children or cognitively impaired
- Report of signs/impacts that are reliably detected
  - Seizure frequency
  - Crying episodes
  - Cough
  - Activity level
Clinician Reported Outcome (ClinRO)

- Involves clinical judgement/interpretation of the condition
- Rated by a trained health-care professional based on observation/interview
- Unable to assess symptoms known only to the patient
  - Useful when patient unable to self-report
  - Patient unable to comment on a specific sign

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**Scale for the assessment and rating of ataxia (SARA)**

<table>
<thead>
<tr>
<th>Score</th>
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<tr>
<td>1</td>
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1. **Gait**
   - Patient is asked (1) to walk at a safe distance parallel to a wall including a half turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.
   - Normal: no difficulties in walking, turning, and walking tandem (up to one meter allowed).
   - Slight difficulties: only visible when walking 10 consecutive steps in tandem.
   - Moderate: walking 10 steps not possible.
   - Severe: staggering, difficulties in half-sit, but with support.
   - Very severe: permanent support of one stick or light support by another.

2. **Stance**
   - Patient is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heels and toes).
   - Normal: does not move except, eyes are open. For each condition, three trials are allowed. Best trial is used.
   - Normal, able to stand in tandem for >10s.
   - Normal, able to stand with feet together without movement, but not in tandem for >10s.
   - Able to stand with feet together for >10s, but only with arm.
   - Able to stand for 10s without support in natural position, but not with feet together.
   - Able to stand for 10s in natural position only with intermittent support.
   - Able to stand >10s in natural position only with constant support of one arm.
   - Unable to stand for >5s, with constant support of one arm.

3. **Sitting**
   - Patient is asked to sit on an armchair and then sit with both hands behind the back. (1) without support of free, open shoulders and arms, constrained to the back.
   - Normal: no difficulties sitting >10s.
   - Slight difficulties, intermittent.
   - Severe: able to sit for >10s only with intermittent support.
   - Very severe: unable to sit for >10s with continuous support.

4. **Speech disturbance**
   - Speech is assessed during normal conversation.
   - Normal: no difficulties.
   - Suggestion of speech disturbance.
   - Inspected speech, but not easy to understand.
   - Occasional words difficult to understand.
   - Many words difficult to understand.
   - Only single words understandable.
   - Speech unintelligible/inaudible.

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Understanding Glut1 DS
Symptoms and Functional Impact
How do we learn about Glut1 DS?

• Literature review
  – Heterogeneous and complex in symptom presentation
  – Spectrum of paroxysmal manifestations is broad
  – Seizure type and movement disorders are well described
  – Limited information about functional impact in medical literature

• Clinician interviews

• Patient and Caregiver perspective
  – Concept elicitation
    • Patient experience in their own words
  – Evaluation/Observation study
Clinician Interviews\(^1\): Movement Disorders

- Broad range of movement disorder symptoms reported
  - Continuous and paroxysmal
- Frequency of paroxysmal attacks is variable
- Symptom severity range from mild-severe
  - Severe symptoms are disabling
- Fasting, exercise, infections, high temperatures, tiredness trigger paroxysmal symptoms
- Fine motor function, walking ability, physical activity, and activities of daily living affected

\(^1\)Interviews part of Ultragenyx sponsored study UX7385 conducted by Adelphi Values
Patient/Caregiver Qualitative Study

- Glut1 DS patient/caregiver n=10
- Age range of Glut1 DS patients: 5-58 years old
- Interview
  - Please tell us about the movement disorder symptoms that are experienced
  - How do these movement disorders affect activities of daily life?
  - Are there any things that are difficult to do because of movement disorder symptoms?
  - How do you deal with these impacts in day to day life?
Different types of movement disorder symptoms reported by patients/caregivers

- Ataxia
- Dysarthria
- Dystonia
- Myoclonus/Chorea
- Oculomotor
- Hypotonia
- Spasticity
- Tremor

Number of patients

- Paroxysmal
- Continuous

n=10
Impact of movement disorders reported by patients/caregivers

<table>
<thead>
<tr>
<th>Physical</th>
<th>Daily Life</th>
<th>Social</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance/Falling</td>
<td>Dressing</td>
<td>Talking to others</td>
<td>Embarrassed</td>
</tr>
<tr>
<td>Coordination</td>
<td>Eating</td>
<td>Viewed differently</td>
<td>Frustrated</td>
</tr>
<tr>
<td>Walking</td>
<td>Writing</td>
<td>Relationships</td>
<td>Irritable</td>
</tr>
<tr>
<td>Posture</td>
<td>Independence</td>
<td>Avoidance of social participation</td>
<td>Distressed/upset</td>
</tr>
<tr>
<td>Limited mobility/activities</td>
<td>Attention</td>
<td></td>
<td>Lack of confidence</td>
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<tr>
<td>Fatigue</td>
<td></td>
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<tr>
<td>Pain</td>
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</tbody>
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1Data taken from Ultragenyx sponsored study UX7385 conducted by Adelphi Values
Glut1 DS Functional Assessment Study

- Glut1 DS patients n=7
- Age range: 6-32 years old
- Assessments
  - HR-QoL: Medical Outcomes Survey SF-10 (5-17 years old)
  - Walking capacity/endurance: 12 Minute Walk Test
  - Fine and Gross Motor Function
  - Movement Disorder Specific Rating Scales
    - Scale for the Assessment and Rating of Ataxia (SARA)
    - Abnormal Involuntary Movement Scale (AIMS)
  - Actigraphy: Activity level and sleep

1Ultrapgenyx sponsored study UX007G-CL001
Physical health is substantially impaired in children with Glut1 DS.

Mean ± SD
n=5

Normed based score
Mean=50; SD 10
Walking capacity decreased in Glut1 DS

- No paroxysmal exertional dyskinesias were observed during testing
Fine motor precision is affected in Glut1 DS

- Test evaluates precise control of hand movement
- Able to differentiate between subjects with and without impaired motor function
Limitations of movement disorder rating scales to capture paroxysmal symptoms

- Scale for the Assessment and Rating of Ataxia (SARA)
  - Maximum score = 40; higher scores = increased ataxia
    - Glut1 DS: mean SARA score 7/40
- Abnormal Involuntary Movement Scales (AIMS)
  - 10 items; 0-4 severity rating scale
  - Positive score = score ≥2 on two items or ≥3 on 1 item
  - Only 2/7 Glut1 DS patients with positive AIMS score
- Variable frequency of Glut1 DS paroxysmal movement disorder symptoms limit the use of rating scales during a clinic visit
Activity levels are reduced in Glut1 DS\textsuperscript{1}

\textsuperscript{1}Data taken from Ultragenyx sponsored study UX007G-CL001
Qualitative Research Findings

• Movement disorder events affect/limit physical functioning and activities of daily living
  – Paroxysmal events were not directly observed during study visit
  – In-clinic tests reflect baseline functional status
• Physical health substantially impaired in Glut1 DS
• All patients exhibited an impaired ability to walk
• Activity levels lower in Glut1 DS patients
Qualitative Research Conclusions

• Paroxysmal manifestations of Glut1 DS impact physical functioning and activities of daily living
• A daily diary is an appropriate tool to capture paroxysmal Glut1 DS events which may not present during a clinic visit
• In-clinic assessments such as walking tests can be used to assess functional capacity/energy deficiencies associated with Glut1 DS
Glut1 DS Symptom Diary: A Novel Endpoint

• How many movement disorder events did you experience that affected/limited your ability to perform everyday activities in the past 24 hours?
• Approximately how many minutes/hours did the movement disorder event last?
• Which of the following activities were affected/limited by the movement disorder event?
• Please list the symptoms you experienced during the movement disorder event
Clinical Outcome Assessment

Selection for Glut1 DS Clinical Trials
## Glut1 DS Endpoint Model

<table>
<thead>
<tr>
<th>Concept</th>
<th>Assessment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure frequency</td>
<td>Seizure Diary</td>
<td>Reduction in seizure frequency</td>
</tr>
<tr>
<td>Movement Disorder frequency</td>
<td>Movement Disorder Diary</td>
<td>Reduction in movement disorder frequency</td>
</tr>
<tr>
<td>Impaired walking capacity</td>
<td>6/12 Minute Walk Test</td>
<td>Increased walk test distance</td>
</tr>
<tr>
<td>Physical Functioning/Activities of Daily Living</td>
<td>Health Related-Quality of Life questionnaire</td>
<td>Improved Health Related-Quality of Life</td>
</tr>
<tr>
<td>Self care, productivity and leisure performance</td>
<td>Canadian Occupational Performance Measure</td>
<td>Improved performance</td>
</tr>
<tr>
<td>Participation in physical activities</td>
<td>Activity Monitor</td>
<td>Increased activity levels</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Cognitive testing</td>
<td>Improved mental/motor speed, episodic memory, executive function</td>
</tr>
</tbody>
</table>
Glut1 DS Clinical Trials and Initiatives

- Randomized, double-blind, placebo-controlled study to assess the safety and efficacy of UX007: *Enrollment complete; results expected end of 2016/early 2017*
- Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of UX007 for movement disorders: *Study start end of 2016*
- Open label study to assess the safety and efficacy of UX007 in combination with the ketogenic diet: *In Development*
- Online questionnaire to further understand Glut1 DS: *In Development*

For more information, go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Acknowledgements

• To the patients and families who participated in the qualitative research initiatives and clinical trials
Glut1DSinFocus.com

Glut1 DS In Focus

No-cost genetic testing
Check for mutations that could cause Glut1 DS

GET STARTED

Glut1 DS is a rare genetic disease.

Glucose transporter type-1 deficiency syndrome (Glut1 DS) is a rare disease that was first discovered in 1991 and is thought to affect between 3000 and 7000 people in the United States. For most, it is caused by mutations in the SLC2A1 gene.\textsuperscript{1,2}

Glut1 DS In Focus is devoted to the education and awareness of Glut1 DS for patients, caregivers, and health care providers, as well as advancing research to treat this disease.

www.ultragenyx.com
UltraRareAdvocacy.com

What is Patient Advocacy?

Patient advocacy serves as a point of connection between the patient community and a company or organization.

Welcome

At Ultragenyx, the patient advocacy team is passionate about educating and supporting you: patients, families and caregivers affected by rare and ultra-rare diseases. Through this site you can find valuable resources, hear from others who live with rare diseases, and learn more about our commitment to the rare disease patient community.
Thank you!

- Contact patientadvocacy@ultragenyx.com with questions
The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests. The documents must be available at the Provider offices for at least 5 years.

Conflict of Interests Declaration

Undersigned ___________________________________________ as:

☐ scientific responsible  ☐ moderator  ☐ teacher  x speaker  ☐ tutor

of the event “1st European Conference on Glut1 Deficiency”
Milan - Italy, 7th-8th October 2016

Based on Art.. 3.3 about the Conflict of Interests, page 18,19 of the State-and-Region Agreement dated 19 April 2012, managed by Biomedia n. 148

Declares

☐ that in the last two years DIDN’T have any relationships about comercial financings with people having conflict of interests in the health field

x that in the last two years HAD relationships about comercial financings with people having conflict of interests in the health field
(please specify the names):

Ultagenyx Pharmaceutical Inc. ___________________________________________  ___________________________________________
_________________________________________  ___________________________________________
_________________________________________  ___________________________________________
The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests. The documents must be available at the Provider offices for at least 5 years.

**SLIDE N.2**

Undersigned

First name Alexandra Surname Bowden

Declares, under his responsibility, that in the report entitled

“Approaches to Evaluating UX007 (Triheptanoin) in Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)”

There will be named the following Companies and / or Commercial Products:

Ultragenyx Pharmaceutical Inc.

UX007 or Triheptanoin

JUST WITH AN EDUCATIONAL AND SCIENTIFIC AIM OR TO REFER TO NATIONAL OR INTERNATIONAL GUIDELINES